

REMARKS

This application relates to antimicrobial agents. Lactoferrin (LF) is a known antimicrobial agent. It is a glyco-protein having a bilboate structure, with a positively charged N-terminus lobe and a negatively charged C-terminus lobe. The activity of LF is highly dependent on its three-dimensional or tertiary structure. If the protein does not have the proper conformation, its activity is diminished or lost.

Now it has been unexpectedly found that LF can be stabilized and its antimicrobial activity increased, if the LF is immobilized by binding its N-terminus to a suitable, naturally occurring substrate. The LF can be immobilized by mixing the LF with the naturally occurring substrate in a suitable medium, such as deionized water.

As is readily understood by the skilled artisan, not all naturally occurring materials are suitable substrates. For example, an inert material, such as the long-chain hydrocarbons, paraffin oil and Vaseline, do not have the functionality required to bind the positively-charged N-terminus. Moreover, multifunctional materials, including emulsifiers, such as lecithin, bind to the LF in areas other than the N-terminus, thus altering the protein's tertiary structure and adversely affecting its antimicrobial activity.

The examiner renumbered originally numbered claims 78 through 205 as 75-202, respectively. The examiner then requested that the claim dependencies of the re-numbered claims be amended in order to reflect the renumbered claim numbers. As can be seen by the above amendments, this has been done.

The examiner objected to the claim for priority, because it was not the first sentence of the specification and because it did not use the appropriate language. As can

be seen by the above amendments, the position and wording of the claim for priority has been changed, so that this ground for objection has been overcome.

The examiner rejected claims 4, 28-30, 37, 86-88, 99, and 100 under 35 U.S.C. § 112, second paragraph, as being indefinite. The examiner rejected dependent claim 4, because there was no antecedent basis for the phrase “naturally occurring substrate not including gelatin.” As can be seen by the above amendments, this phrase has been added to independent claim 1, so that this ground for rejection has been overcome.

The examiner rejected dependent claim 28, because there was no antecedent basis for the phrase “the aqueous solution.” As can be seen by the above amendments and as suggested by the examiner, claim 28 has been amended to depend from claim 22, which includes this phrase, so that this ground for rejection has been overcome.

The examiner rejected dependent claim 30, because there was no antecedent basis for the phrase “The composition in accordance with claim 29.” As can be seen by the above amendments, this phrase has been amended to recite “The method in accordance with claim 29,” so that this ground for rejection has been overcome.

As can be seen by the above amendments and as requested by the examiner, at claim 37, line 3 “or” has been changed to “and.” The examiner rejected dependent claim 86, because there was no antecedent basis for the phrase “The composition in accordance with claim” 85. As can be seen by the above amendments, this phrase has been amended to recite “The foodstuff in accordance with claim 85,” so that this ground for rejection has been overcome. Finally, as suggested by the examiner, claims 99 and 100 have been amended so that they depend on claim 98. Therefore, this ground for rejection has also been overcome.

The examiner objected to claims 6, 36, 39, 80, 87, 99, 100, 146, 155, and 163 on the basis of various informalities. As can be seen by the above amendments, all the informalities have been corrected, so that all of these grounds for objection have been overcome.

The examiner objected to claim 88 under 37 CFR 1.75(c) as being of improper dependent form. As can be seen by the above amendments and as suggested by the examiner, claim 88 has been amended to depend on claim 86, so that this ground for rejection has been overcome.

The examiner rejected claims 1-49, 51, and 56-202 based on the doctrine of obviousness-type double patenting over U.S. Patent No. 6,172,040. Enclosed is a terminal disclaimer in compliance with 37 CFR 1.321(c), so that this ground for rejection has been overcome.

The examiner rejected claim independent claim 1, dependent claims 2, 3, 5, 11, independent claim 18, dependent claims 19, 20, 22, and 31, independent claim 101, independent claim 102 and dependent claims 103, 104, 106, 115, 119-129, 131, 132, 134, 136-138, 142-151, 153, 197, and 200-202 under 35 USC §102(b) as being anticipated by RU 2,099,065 A. For a prior art reference to anticipate, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990).

RU 2 099 065 A discloses a gel preparation containing LF immobilized in gelatin. The resulting gel is used to treat the oropharyngeal region and the esophagus of onocological patients who have received radiation or chemical radiation treatments. As can be seen by the above amendments, independent claims 1, 18, 101 and 102 have been amended to specifically exclude gelatin. Therefore, none of claims 1-3, 5, 11, 18-20, 22, 31 101-104,

106, 115, 119-129, 131, 132, 134, 136-138, 142-151, 153, 197, and 200-202 are anticipated by this reference.

The examiner rejected claims 1, 2, 11, 18, 19, 28, 31, 39, 101-103, 119-124, 126-129, 131, 132, 134, 142-151, 153, 164, 171-173, 175, 186, 193-195, 197, and 200 under 35 USC §102(b) as being anticipated by or under 35 USC §103(a) as obvious in view of WO Patent Application 91/13982 ("WO Patent Application '982"). WO Patent Application '982 generally relates to human LF expressed using recombinant DNA. It discloses the use of this LF as a nutritional supplement, an antiseptic, and as a food-spoilage retardant. The LF can be compounded with certain carriers or diluents.

However, WO Patent Application '982 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF. The examiner asserts that:

"The WO Patent Application '982 teaches LF in combination with stearic acid (which is a lipid and also corresponds to Applicant's pharmaceutically acceptable carrier of claim 102) or its salts . . . Because the same components are present in the same defined dispersion, inherently the LF in the composition of the WO Patent Application '982 will be immobilized via its N-terminus . . ."

Applicant respectfully disagrees. The *mere presence* in a mixture of LF and stearic acid or any of the other naturally occurring carriers or diluents taught in WO Patent Application '982 would *not* inherently result in immobilization of the LF via its N-terminus.

The reference does not disclose or suggest any conditions under which the compounds could be mixed to achieve such immobilization. Merely compounding solid LF with a solid stearic acid carrier will not provide an environment suitable to cause the LF to become immobilized via its N-terminus region. Instead, appropriate conditions must be chosen before immobilization can occur. As described in the instant application, LF is immobilized by first mixing the LF with the naturally occurring substrate *in a suitable medium*, such as deionized water. Therefore, the rejection of claims 1, 2, 11, 18, 19, 28, 31, 39, 101-103, 119-124, 126-129, 131, 132, 134, 142-151, 153, 164, 171-173, 175, 186, 193-195, 197, and 200 as being anticipated by or as obvious in view of WO Patent Application '982 should be withdrawn.

The examiner rejected claims 1, 2, 5, 18, 19, 22, 31, 38, 39, 101-103, 106, 115-117, 119-124, 126-129, 131-132, 134, 136, 142-151, 153, 164, 171-173, 175, 186, 193-197, and 200-202 under 35 USC §102(b) as being anticipated by or under 35 USC §103(a) as obvious in view of European Patent Application 753,309 (European Patent Application '309). European Patent Application '309 generally relates to the preparation of mixtures of lactoferrin and desferrioxamine methanesulphonate useful for the therapy of viral infectious diseases.

However, European Patent Application '309 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF. The examiner asserts that:

"The European Patent Application '309 teaches compositions comprising LF and carriers such as paraffin oil and Vaseline (which are lipids), xantan gum and corn starch (which are polysaccharides), and lecithin (which is an emulsifier). . . .

Because the same components are present in the same defined dispersion, inherently the LF in the composition of the European Patent Application '309 will be immobilized by its N-terminus . . . "

Applicant respectfully disagrees. The *mere presence* in a mixture of LF and any of the other naturally occurring carries taught in European Patent Application '309 would *not* inherently result in immobilization of the LF via its N-terminus. For example, paraffin oil and Vaseline are long chain hydrocarbons which will not bind LF's positively charged N-terminus. Similarly, corn starch and xanthan are neutral, polysaccharide, thickening agents that will not bind LF's N-terminus. On the other hand, emulsifiers, such as lecithin contain multiple functional groups and will bind LF in areas other than the N-terminus, thus altering the protein's tertiary structure and adversely affecting its antimicrobial activity. Therefore, the rejection of claims 1, 2, 5, 18, 19, 22, 31, 38, 39, 101-103, 106, 115-117, 119-124, 126-129, 131, 132, 134, 136, 142-151, 153, 164, 171-173, 175, 186, 193-197, and 200-202 as being anticipated by or as obvious in view of European Patent Application '309 should be withdrawn.

The examiner rejected claims 1, 2, 5, 18, 19, 22, 31, 32, 38, 39, 101-103, 106, 115, 119-124, 126-129, 131-136, 142-151, 153, 162-165, 171-173, 181, 184-187, 193-197, and 200-202 under 35 USC §102(b) as being anticipated by or under 35 USC

§103(a) as obvious in view of European Patent Application 753,308 (European Patent Application '308).

European Patent Application '308 generally relates to the use of LF for therapy of diseases caused by Gram positive pathogen microorganisms. However, European Patent Application '308 neither broadly teaches LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor does it provide a specific example of such an immobilized LF. The examiner asserts that:

"The European Patent Application '308 teaches compositions comprising LF and peppermint oil, gum base and corn starch (which are polysaccharides) . . .

Because the same components are present in the same defined dispersion, inherently the LF in the composition of the European Patent Application '308 will be immobilized via its N-terminus . . . "

Applicant respectfully disagrees. The *mere presence* in a mixture of LF and any of the other ingredients taught in European Patent Application '308 would *not* inherently result in immobilization of the LF via its N-terminus. For example, peppermint oil and other flavoring agents will not bind LF's N-terminus bind LF, so as to preserve the protein's tertiary structure and enhance its antimicrobial activity. Similarly, gum base and corn starch are neutral, polysaccharide, thickening agents that will not bind LF's N-terminus. Therefore the rejection of claims 1, 2, 5, 18, 19, 22, 31, 32, 38, 39, 101-103, 106, 115, 119-124, 126-129, 131-136, 142-151, 153, 162-165, 171-173, 181, 184-187,

193-197, and 200-202 under 35 as being anticipated by or as obvious in view of European Patent Application '308 should be withdrawn.

The examiner rejected claims 1-3, 5, 18-20, 22, 31, 32, 102-104, 106, 115, 119, 124, 137, 138, 142-150, 154, 164, and 165 under 35 USC § 102(e) as being anticipated by US Patent 6,066,469 by Kruzel *et al.* ("Krutzel *et al.*"). This patent is similar to WO Patent Application '982. Both references claim priority based on the same US patent application. Consequently, just as with WO Patent Application '982, Krutzel *et al.* neither broadly teach LF immobilized on a naturally occurring substrate via the N-terminus region of the LF, nor provide a specific example of such an immobilized LF. The examiner asserts that:

"Krutzel *et al.* teach nutritional supplements comprising LF in combination with adjuvants or diluents such as cellulose, starch, tragacanth, and sodium carboxymethylcellulose. . . . Because the same components are present in the same defined dispersion, inherently the LF in the nutritional supplements of Kruzel et al will be immobilized via its N-terminus . . . "

Applicant respectfully disagrees. The *mere presence* in a mixture of LF and any of the adjuvants or diluents taught in WO Patent Application '982 would *not* inherently result in immobilization of the LF via its N-terminus. For example, starch is a neutral, polysaccharide, thickening agent that will not bind LF's N-terminus. On the other hand, tragacanth contains multiple functional groups and will bind LF in areas other than the N-

terminus, thus altering the protein's tertiary structure and adversely affecting its antimicrobial activity.

Furthermore, the reference does not disclose or suggest any conditions under which the compounds could be mixed to immobilization. Merely compounding solid LF with a solid adjuvant or diluent will not provide an environment suitable to cause the LF to become immobilized via its N-terminus region. Instead, appropriate conditions must be chosen before immobilization can occur. As described in the instant application, LF is immobilized by first mixing the LF with the naturally occurring substrate *in a suitable medium*, such as deionized water. Therefore, the rejection of claims 1-3, 5, 18-20, 22, 31, 32, 102-104, 106, 115, 119, 124, 137, 138, 142-150, 154, 164, and 165 as being anticipated by Kruzel *et al.* should be withdrawn.

The examiner rejected claims 1-3, 5, 11, and 98-101 under 35 USC §102(b) as being anticipated by the Harper *et al.* in view of Okonogi *et al.* (US Patent 4,791,193). Harper *et al.* teaches that milk contains, *inter alia*, naturally occurring substrates such as casein, triglycerides, lactose, α -lactalbumin, IgA, lysosome, and nucleic acids. Okonogi *et al.* teach that milk contains LF. The examiner argued that, "Because the same components are present in the same aqueous solution, inherently the LF in milk will be immobilized" As can be seen by the above amendments, independent claims 1 and 101 have been amended to recite that the LF is *isolated* LF. Therefore, the rejection of claims 1-3, 5, 11, and 98-101 has been overcome.

Finally, the examiner rejected claims 1-3, 5, 11, and 98-101 under 35 USC §102(b) as being anticipated by the Harper *et al.* in view of Okonogi *et al.* and the Naidu *et al.* article. The Naidu *et al.* article is cited because, "it teaches that LF complexes with

casein, α -lactalbumin, lysozyme, and IgA (see page 45, first full paragraph), and thus is further evidence that the milk of the Harper *et al.* text inherently comprises immobilized LF." Again, as can be seen by the above amendments, independent claims 1 and 101 have been amended to recite that the LF is *isolated* LF. Therefore, the rejection of claims 1-3, 5, 11, and 98-101 has been overcome.

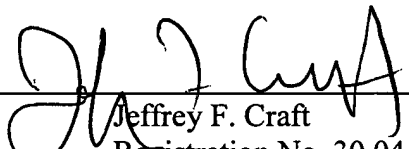
CONCLUSION

In light of the foregoing amendments, remarks and terminal disclaimer, it is believed that the application is in condition for allowance, so that a prompt and favorable action is respectfully requested.

Respectfully submitted,

SONNENSCHN NATH & ROSENTHAL

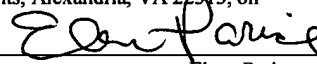
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